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Working Paper on toxicity of chemical warfare agents

Modern lethal chemical warfare agents are exceedingly toxic substances, much more toxic for the most part than the chemicals in common industrial use. Because of this difference, it has been suggested that the degree of toxicity is a logical choice as one possible criterion for defining chemical warfare agents for the purpose of an arms control agreement.

As noted in the work programme presented by the United States delegation (CCD/360), there are several different approaches to the question of definition, each with its own advantages and disadvantages. A criterion based on a toxicity limit would have the advantage of being directly related to the potential danger from a particular substance. It would be applicable to known super-toxic substances or any super-toxic substance discovered in the future. However, compounds which are less toxic might still have utility either as chemical warfare agents or agent precursors. Among these are mustard-type compounds, dual-purpose agents such as phosgene (carbonyl chloride), hydrogen cyanide, and cyanogen chloride, and binary precursors. If a prohibition is to cover all lethal agents it might be necessary to adopt a general-purpose criterion and perhaps other criteria in addition to a toxicity criterion.

Considerable progress has already been made in working out the technical aspects of a practical toxicity criterion. Concrete proposals for a toxicity criterion have already been presented by the delegations of Japan (CCD/301, CCD/374) and Canada (CCD/387, CCD/414). Both delegations adopted a similar approach by proposing a criterion based on the toxicity of a particular agent. Soman was suggested as a "boundary agent" by the Japanese delegation and tabun by the Canadian delegation.

As our delegation and others have noted, a toxicity value for a compound is meaningful only if the experimental conditions under which it was measured are specified in detail. For this reason, in order to establish a practical toxicity criterion, it would be necessary to define not only the toxicity level, but also the animal to be used for measurement and the route by which the chemical is administered.

Experimental Animal

The military utility of CW agents is related to toxicity to humans. Theoretically a toxicity criterion would be based on human reactions to chemical agents. Obviously, however, experimental animals must be used instead to measure the toxicity values.

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In general, the assumption that a compound that is super-toxic to experimental animals will will also be very dangerous to humans is a sound one. In toxicological studies, a variety of different animals are commonly used. As noted in Table 1, toxicity values vary somewhat from one species to another. Therefore, a toxicity threshold must be tied to a specific animal.

Table 1. Toxicity of Tabun to Experimental Animals*/

Animal	LD_{50} (mg/kg)**/
Mouse	0.35 - 0.40
Rat	0.16
Guinea Pig	0.13 - 0.3
Rabbit	0.3 - 0.5
Cat	0.10
Goat	0.3

*/ Subcutaneous administration: United States Army data

**/ The LD_{50} is the dose which is lethal to 50 per cent of a group of animals (median lethal dose).

Route of Administration

The toxicity of an agent may vary depending on the route by which it is administered to the test animal. Chemicals are commonly administered orally or by inhalation or introduced directly by injection ("parenteral" administration). The most common parenteral routes of administration are into a blood vein (intravenous), into the abdominal fluid (intraperitoneal), into a muscle (intramuscular) or beneath the skin (subcutaneous). Percutaneous administration involves application on the skin. The variation in toxicity with route of administration is illustrated for tabun in Table 2.

Table 2. Influence of Route of Administration on Toxicity of Tabun */

Route of Administration	LD_{50} (mg/kg)
Intravenous	0.10 - 0.15
Intraperitoneal	0.66 - 0.9
Subcutaneous	0.35 - 0.40
Percutaneous	1.0 - 2.8

*/ Taking a mouse as the experimental animal; United States Army data.

Unfortunately, it is not possible to convert the value obtained by one route of administration to an equivalent value for a different route. As shown in Table 3, the relative values for different routes of administration vary from compound to compound.

Since the military potential of super-toxic compounds is often closely related to their inhalation toxicity, it would seem logical to establish a criterion based on inhalation toxicity as proposed in CCD/414. Some chemicals, however, are not super-toxic when inhaled, but would be extraordinarily toxic if they were carried into the body by a projectile which penetrated the skin. Included in this category are super-toxic carbamates. For this reason a criterion based on inhalation toxicity would not be sufficient.

The toxicity criteria proposed in CCD/374 are based on subcutaneous or intra-peritoneal injection. These routes of administration are generally applicable to any compound and are less difficult from a technical standpoint than administration by the respiratory route.

It would be possible to supplement a criterion based on inhalation toxicity with one derived from parenteral toxicity. However, it would be simpler to rely on parenteral toxicity alone, since any compound that is super-toxic on inhalation will also be super-toxic by a parenteral route.

To some extent the selection of a particular experimental animal and a given parenteral route of administration in defining the criterion is arbitrary. The choice might best be made simply according to the relative amount of data available for the different situations. It appears that more data, particularly on known CW agents, are available for the mouse (subcutaneous administration) than for other animals and other routes of administration listed in Table 4.

Judging from the data in Table 4, there appears to be little overlap between single-purpose super-toxic CW agents and dual-purpose chemicals. Ideally, the toxicity criterion should be defined so as to separate the two groups cleanly. It probably will be impossible to do so. However, establishing an LD_{50} value of 0.50 mg/kg (mouse; subcutaneous administration) as the limit, as suggested in CCD/301, or a value close to 0.50 mg/kg, may be the optimal solution to the problem of selecting a suitable level.

Experimental Variability

In order for toxicity measurements from different laboratories to be consistent with each other, the detailed experimental procedures must be standardized. Some of the conditions which would have to be established are listed in CCD/374. If general agreement were reached to adopt a prohibition based on a specific toxicity threshold, the precise experimental procedures could undoubtedly be worked out by experts in toxicology.

Table 3. Relative Toxicity Values for Several Results of Administration */

Route of Administration	Procaine LD_{50} (mg/kg) (Mouse)	Procaine Relative Value	Isoniazid LD_{50} (mg/kg) (Mouse)	Isoniazid Relative Value	DFP **/ LD_{50} (mg/kg) (Rabbit)	DFP **/ Relative Value	Pentobarbital LD_{50} (mg/kg) (Mouse)	Pentobarbital Relative Value
Intravenous	45	1	153	1.0	0.34	1.0	80	1.0
Intraperitoneal	230	5	132	0.9	1.00	2.9	130	1.6
Intramuscular	630	14	140	0.9	0.85	2.5	124	1.5
Subcutaneous	800	18	160	1.0	1.00	2.9	130	1.6
Oral	500	11	142	0.9	4 to 9	11.7 to 26.5	280	3.5

*/ from T.A. Loomis, Essentials of T xicology, Lea and Febiger, Philadelphia, 1968.

**/ DFP = diisopropylfluorophosphate

Table 4. Mouse Toxicity Data (Subcutaneous Administration)

Compound */	Toxicity (LD_{50}, mg/kg)	Source
3152 CT (carbamate)	0.005 (i.v., dog)	Funke, Depierre and Krucker, 1952
VX	0.022	U.S. Army
VE	0.025	U.S. Army
VM (edemo)	0.035	U.S. Army
VS	0.035	U.S. Army
GB (sarin)	0.04	CCD/374
GB (sarin)	0.06 - 0.15	CCD/374
GD (soman)	0.1	CCD/374
GF	0.11 - 0.20	U.S. Army
GD (soman)	0.125	U.S. Army
GB (sarin)	0.15	U.S. Army
VG (amiton, tetram)	0.155 (male)	U.S. Army
GB (sarin)	0.173	CCD/374
GB (sarin)	0.2	CCD/374
GB (sarin)	0.214	Askew, 1957
GB (sarin)	0.22	CCD/374
GE (ethly sarin)	0.301	U.S. Army
GA	0.35 - 0.40	U.S. Army
neostigmine (prostigmine) **/	0.42	U.S. Army
echothiophate **/	0.50	Schaumann, 1960
neostigmine methylsulfate **/	0.51	Brown et al, 1950
neostigmine iodide **/	0.55	Brown et al, 1950
paraoxon **/	0.6 - 0.8	CCD/374
paraoxon **/	0.7	Augustinsson, 1953; Schaumann, 1960
neostigmine (prostigmine) **/	0.8	Toxic Substances List, 1973
TEPP (tetraethylpyrophosphate) **/	0.85	U.S. Army
HN-1	1.1 - 2.05	U.S. Army
physostigmine salicylate **/	1.24	Brown et al, 1950
paraoxon-ME **/	1.4	CCD/374
HN-3 **/	2.01 (HCl)	U.S. Army
colchicine **/	2.3 - 3.8	U.S. Army

Mouse Toxicity Data (Subcutaneous Administration)

Compound	(Toxicity (LD_{50}, mg/kg)	Source
metasystox (methyldemeton) **/	2.9 - 3.3	CCD/374
potassium cyanide **/	2.9 - 6.0	U.S. Army
DFP **/	3.2 - 4.7	U.S. Army
DFP **/	4	Toxic Substances List, U.S. Dept. of HEW, 1973
HN-2 **/	4.5	U.S. Army
methyl fluorcacetic acid **/	5 - 19	U.S. Army
sulfotepp **/	8	CCD/374
parathion **/	10 - 12	CCD/374
parathion **/	"	Holmstedt, 1963
mustard gas (H)	20 - 30	U.S. Army
methylparathion **/	30	Helmstedt, 1963
cyanogen chloride (CK) **/	39	U.S. Army

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*/ The structures of military CW agents listed here are given in CCD/365.

**/ Commercial chemicals

However, even if procedures are standardized, there will be a certain amount of variability in the measurements. It is to be expected that two laboratories using identical samples of chemical will still obtain slightly different toxicity values. This is because it is difficult to control precisely all the variables involved in making toxicity tests on animals.

In making toxicity measurements, a range of 20 per cent on either side of the average value is usually considered good. Studies on the reproducibility of oral toxicity values have demonstrated that a broader range should normally be expected. The ratio of the highest to lowest value is likely to be between 1.5 and 3 for oral toxicity values and may be as high as 10. (For parenteral toxicity values, the range may be somewhat smaller). Usually, the LD_{50} value reported is the average of a range of values.

The variability of toxicity values could pose a problem in applying a treaty prohibition in certain cases. Normally only one or two independent values will be available, and it is quite possible that these values will differ greatly from the average value that would be obtained from a large number of independent determinations. For a particular compound, one laboratory might report the compound to be more toxic than the limit while a different laboratory might conclude that it is less toxic.

This difficulty may be illustrated by assuming that the toxicity criterion has been defined to be an LD_{50} of 0.50 mg/kg (mouse; subcutaneous administration) and that a standardized experimental procedure has been adopted. For a compound with an average LD_{50} value of 0.36 mg/kg, which is below the limit, the possible results from different laboratories range approximately from 0.18 mg/kg to 0.54 mg/kg. If the value reported is greater than 0.50 mg/kg, it might be argued that the compound should not be prohibited. Analogously, for a compound which would have an average LD_{50} value of 0.80 mg/kg, which is well above the 0.50 mg/kg limit, a single laboratory might report a value as low as 0.40 mg/kg. In this case, prohibition might well be advocated.

Obviously, some differences may arise about application of the prohibition to a specific compound even if a toxicity criterion is established. One possible way to help resolve such differences would be to have an appropriate independent laboratory measure the toxicity.

Super-Toxic Dual-Purpose Compounds

As noted above, it is unlikely that a toxicity criterion can be found that will cleanly separate single-purpose super-toxic CW agents from dual-purpose chemicals. A few dual-purpose compounds are likely to be more toxic than the limit established by the toxicity criterion. The data in Table 4 indicate that most of these compounds will be drugs. Strict application of the toxicity criterion would lead to a ban on

these super-toxic dual-purpose compounds. However, super-toxic drugs are produced in very small quantities and are not well suited as chemical warfare agents. It might be useful to consider application of the criterion in such a way that super-toxic drugs would not be prohibited. This might be accomplished by allowing super-toxic chemicals to be produced in quantities necessary for legitimate use as a drug if the use as a drug had been demonstrated beforehand.